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WO 2004/096826 A3

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C07H 21/00, A61K 47/48
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MI2003A000860 29 April 2003 (29.04.2003) IT
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- (81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:
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— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- (88) Date of publication of the international search report:
26 May 2005
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: METHOD FOR SELECTIVE INHIBITION OF HUMAN N-MYC GENE IN N-MYC EXPRESSING TUMORS THROUGH ANTISENSE AND ANTIGEN PEPTIDO-NUCLEIC ACIDS (PNA)

(57) Abstract: The present invention refers to sense and antisense peptido-nucleic acids (PNAs). The present invention further refers to the use of said PNAs for preparing drugs for treating genetic diseases.



WO 2004/096826 A3

INTERNATIONAL SEARCH REPORT

Inter application No
PCT/IB2004/001297

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/11 C07H21/00 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SUN LICHUN ET AL: "Antisense peptide nucleic acids conjugated to somatostatin analogs and targeted at the n-myc oncogene display enhanced cytotoxicity to human neuroblastoma IMR32 cells expressing somatostatin receptors" PEPTIDES (NEW YORK), vol. 23, no. 9, September 2002 (2002-09), pages 1557-1565, XP002322720 ISSN: 0196-9781	1-12
Y	the whole document * figure 1: DC-46-9, DC-44-79 and DC-46-3 targeting the 5'UTR terminus; JF-08-69 and JF-08-67 targeting the coding region close to the start site at position 1659-1670 * ----- -/-	2,7

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

31 March 2005

Date of mailing of the international search report

12/04/2005

Name and mailing address of the ISA
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Gohlke, P

INTERNATIONAL SEARCH REPORT

Inter publication No
PCT/IB2004/001297

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DOYLE DONALD F ET AL: "Inhibition of gene expression inside cells by peptide nucleic acids: Effect of mRNA target sequence, mismatched bases, and PNA length" BIOCHEMISTRY, vol. 40, no. 1, 9 January 2000 (2000-01-09), pages 53-64, XP002187945 ISSN: 0006-2960 abstract	1-6,8-12
Y	----- GALDERISI, U. ET AL: "Antisense inhibitory effect: a comparison between 3'-partial and full phosphorothioate antisense oligonucleotides" JOURNAL OF CELLULAR BIOCHEMISTRY (1999), 74(1), 31-37 CODEN: JCEBD5; ISSN: 0730-2312, vol. 74, 1999, pages 31-37, XP002219271 abstract page 32, left-hand column, lines 1-5 page 32, left-hand column, last paragraph	1,3-12
Y	----- ROSOLEN A ET AL: "ANTISENSE INHIBITION OF SINGLE COPY N-MYC EXPRESSION RESULTS IN DECREASED CELL GROWTH WITHOUT REDUCTION OF C-MYC PROTEIN IN A NEUROEPITHELIOMA CELL LINE" CANCER RESEARCH, vol. 50, no. 19, 1990, pages 6316-6322, XP001205716 ISSN: 0008-5472 abstract page 6316, right-hand column, last paragraph	1,3-12
Y	----- CUTRONA GIOVANNA ET AL: "Effects in live cells of a c-myc anti-gene PNA linked to a nuclear localization signal" NATURE BIOTECHNOLOGY, vol. 18, no. 3, March 2000 (2000-03), pages 300-303, XP002322722 ISSN: 1087-0156 page 300	3-5
Y	----- POOGA M ET AL: "CELL PENETRATING PNA CONSTRUCTS REGULATE GALANIN RECEPTOR LEVELS AND MODIFY PAIN TRANSMISSION IN VIVO" NATURE BIOTECHNOLOGY, NATURE PUB. CO, NEW YORK, NY, US, vol. 16, 1998, pages 857-861, XP000910290 ISSN: 1087-0156 abstract page 860, left-hand column, lines 28-30 ----- -/-	3-5

INTERNATIONAL SEARCH REPORT

Inter - plication No
PCT/IB2004/001297

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SIMMONS C G ET AL: "Synthesis and membrane permeability of pna-peptide conjugates" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 7, no. 23, 2 December 1997 (1997-12-02), pages 3001-3006, XP004136573 ISSN: 0960-894X page 3001, last paragraph page 3002; table 1 -----	3-5
P,X	PESSION ANDREA ET AL: "Targeted inhibition of NMYC by peptide nucleic acid in N-myc amplified human neuroblastoma cells: Cell-cycle inhibition with induction of neuronal cell differentiation and apoptosis." INTERNATIONAL JOURNAL OF ONCOLOGY, vol. 24, no. 2, February 2004 (2004-02), pages 265-272, XP009045755 ISSN: 1019-6439 the whole document -----	1-12

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference U216412WO9	FOR FURTHER ACTION	See item 4 below
International application No. PCT/IB2004/001297	International filing date (<i>day/month/year</i>) 29 April 2004 (29.04.2004)	Priority date (<i>day/month/year</i>) 29 April 2003 (29.04.2003)]
International Patent Classification (IPC) or national classification and IPC 7 C12N 15/11, C07H 21/00, A61K 47/48		
Applicant UNIVERSITA' DEGLI STUDI DI BOLOGNA		

1.	This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).																								
2.	This REPORT consists of a total of 8 sheets, including this cover sheet. In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.																								
3.	<p>This report contains indications relating to the following items:</p> <table style="width: 100%;"> <tr> <td style="width: 10%; text-align: center;"><input checked="" type="checkbox"/></td> <td style="width: 30%;">Box No. I</td> <td style="width: 60%;">Basis of the report</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table>	<input checked="" type="checkbox"/>	Box No. I	Basis of the report	<input checked="" type="checkbox"/>	Box No. II	Priority	<input type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	<input type="checkbox"/>	Box No. IV	Lack of unity of invention	<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	<input type="checkbox"/>	Box No. VI	Certain documents cited	<input type="checkbox"/>	Box No. VII	Certain defects in the international application	<input type="checkbox"/>	Box No. VIII	Certain observations on the international application
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<input type="checkbox"/>	Box No. VIII	Certain observations on the international application																							
4.	The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).																								

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 740 14 35	<table style="width: 100%;"> <tr> <td style="width: 50%;">Date of issuance of this report 04 November 2005 (04.11.2005)</td> <td style="width: 50%;">Authorized officer Idhir Britel</td> </tr> <tr> <td colspan="2">Telephone No. +41 22 338 70 60</td> </tr> </table>	Date of issuance of this report 04 November 2005 (04.11.2005)	Authorized officer Idhir Britel	Telephone No. +41 22 338 70 60	
Date of issuance of this report 04 November 2005 (04.11.2005)	Authorized officer Idhir Britel				
Telephone No. +41 22 338 70 60					

PATENT COOPERATION TREATY

REC'D. 08 APR 2005

From the
INTERNATIONAL SEARCHING AUTHORITY

WIPO

PCT

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/IB2004/001297

International filing date (day/month/year)
29.04.2004

Priority date (day/month/year)
29.04.2003

International Patent Classification (IPC) or both national classification and IPC
C12N15/11, C07H21/00, A61K47/48

Applicant
UNIVERSITA' DEGLI STUDI DI BOLOGNA

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1b/s(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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Authorized Officer

Gohlke, P

Telephone No. +49 89 2399-8549



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2004/001297

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☒ in written format
 - ☒ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☒ furnished subsequently to this Authority for the purposes of search.
3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2004/001297

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	2, 7
	No: Claims	1, 3-6, 8-12
Inventive step (IS)	Yes: Claims	
	No: Claims	1-12
Industrial applicability (IA)	Yes: Claims	1-12
	No: Claims	

2. Citations and explanations

see separate sheet

Section II:

In case the priority claim should be found invalid in the European regional phase, the following citation would constitute prior art in the sense of Rule 64.1 (b)(I). This citation fully anticipates the subject-matter of claims 1-12.

D8: PESSON A. et al.: "Targeted inhibition of NMYC by peptide nucleic acid in N-myc amplified human neuroblastoma cells: Cell-cycle inhibition with induction of neuronal cell differentiation and apoptosis." International Journal of Oncology, vol. 24, no. 2, February 2004 (2004-02), pages 265-272, XP009045755

Section V:

1) Reference is made to the following documents:

D1: SUN LICHUN ET AL: "Antisense peptide nucleic acids conjugated to somatostatin analogs and targeted at the n-myc oncogene display enhanced cytotoxicity to human neuroblastoma IMR32 cells expressing somatostatin receptors" PEPTIDES (NEW YORK), vol. 23, no. 9, September 2002 (2002-09), pages 1557-1565, XP002322720 ISSN: 0196-9781

D2: DOYLE DONALD F ET AL: "Inhibition of gene expression inside cells by peptide nucleic acids: Effect of mRNA target sequence, mismatched bases, and PNA length" BIOCHEMISTRY, vol. 40, no. 1, 9 January 2000 (2000-01-09), pages 53-64, XP002187945 ISSN: 0006-2960

D3: GALDERISI, U. ET AL: "Antisense inhibitory effect: a comparison between 3'-partial and full phosphorothioate antisense oligonucleotides" JOURNAL OF CELLULAR BIOCHEMISTRY (1999), 74(1), 31-37 CODEN: JCEBD5; ISSN: 0730-2312, vol. 74, 1999, pages 31-37, XP002219271

D4: ROSOLEN A ET AL: "ANTISENSE INHIBITION OF SINGLE COPY N-MYC EXPRESSION RESULTS IN DECREASED CELL GROWTH WITHOUT

REDUCTION OF C-MYC PROTEIN IN A NEUROEPITHELIOMA CELL LINE"
CANCER RESEARCH, vol. 50, no. 19, 1990, pages 6316-6322, XP001205716
ISSN: 0008-5472

- D5: CUTRONA GIOVANNA ET AL: "Effects in live cells of a c-myc anti-gene PNA linked to a nuclear localization signal" NATURE BIOTECHNOLOGY, vol. 18, no. 3, March 2000 (2000-03), pages 300-303, XP002322722 ISSN: 1087-0156
- D6: POOGA M ET AL: "CELL PENETRATING PNA CONSTRUCTS REGULATE GALANIN RECEPTOR LEVELS AND MODIFY PAIN TRANSMISSION IN VIVO" NATURE BIOTECHNOLOGY, NATURE PUB. CO, NEW YORK, NY, US, vol. 16, 1998, pages 857-861, XP000910290 ISSN: 1087-0156
- D7: SIMMONS C G ET AL: "Synthesis and membrane permeability of pna-peptide conjugates" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 7, no. 23, 2 December 1997 (1997-12-02), pages 3001-3006, XP004136573 ISSN: 0960-894X
- 2) D1 discloses antisense peptide nucleic acids conjugated to somatostatin analogs and targeted at the M-myc oncogene (see in particular figure 1 and Table 1). These antisense PNA-STTs conjugates display enhanced cytotoxicity to human neuroblastoma IMR32 cells expressing STT receptors. D1 also mentions on page 1558, first paragraph, the conjugation of PNAs to short peptide vectors such as transportan (GWTLSAGYLLGKINLAALAKKIL) or penetratin-1 (RQIKIWFQNRRMKWKK) whereupon cellular uptake is increased.
- D1 therefore fully anticipates the subject-matter of claims 1, 3-6, 8-12.
For these reasons, present application does not meet the requirements of Article 33(2) PCT.
- 3) Claim 2 relates to a specific antisense targeting the 5'UTR region of human N-myc gene, namely 5'-TCCACCCAGCGTCC-3' that is complementary to bp positions 109-124.

According to D2, it is known that PNAs targeted to the terminus of the 5'UTR are potent and sequence-specific antisense agents. They can block binding of the translation machinery. They are therefore selected so as to inhibit the formation of the ribosome.

D1 has selected 3 PNAs targeting the 5'UTR region, namely DC-46-9, DC-44-79, DC-46-3 which match different transcription start sites (represented by a shadowed letter with a star above in figure 1). The subject-matter of present claim 2 differs from D1 only in that a different targeted region has been selected namely the one between the targeted regions of DC-44-79 and DC-46-3 at positions 109-124 having a transcription start site at position 117 (see T*). In view of D1 and D2, the PNA selected in claim 2 is merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed.

Therefore the subject-matter of claim 2 does not appear to involve an inventive step (Article 33(3) PCT).

- 4) Claim 7 relates to a specific sense oligomer that corresponds to the region of N-myc mRNA beginning with the ATG start codon at position 1650 and to the corresponding antisense oligomer: these sequences are well known in the art as inhibitors of N-myc expression resulting in decreased cell growth without affecting levels of c-myc protein (see for example D3 and D4). In view of the advantages of PNAs conjugates as taught by D1, the particular PNAs of claim 7 are merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed.

Therefore the subject-matter of claim 7 does not appear to involve an inventive step (Article 33(3) PCT).

- 5) The applicant's attention is also drawn to citations D5-D7 all disclosing the advantages of nuclear localization signal (NLS) peptides when covalently linked to PNAs resulting in efficient cellular uptake of the PNAs. In particular D5-D7 describes the specific peptides of present claim 5 as carriers of PNAs.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/IB2004/001297